

Neural correlates of the LSD experience revealed by multimodal neuroimaging

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Lysergic acid diethylamide (LSD) is the prototypical psychedelic drug, but its effects on the human brain have never been studied before with modern neuroimaging. Here, three complementary neuroimaging techniques: arterial spin labeling (ASL), blood oxygen level-dependent (BOLD) measures, and magnetoencephalography (MEG), implemented during resting state conditions, revealed marked changes in brain activity after LSD that correlated strongly with its characteristic psychological effects. Increased visual cortex cerebral blood flow (CBF), decreased visual cortex alpha power, and a greatly expanded primary visual cortex (V1) functional connectivity profile correlated strongly with ratings of visual hallucinations, implying that intrinsic brain activity exerts greater influence on visual processing in the psychedelic state, thereby defining its hallucinatory quality. LSD's marked effects on the visual cortex did not significantly correlate with the drug's other characteristic effects on consciousness, however. Rather, decreased connectivity between the parahippocampus and retrosplenial cortex (RSC) correlated strongly with ratings of "ego-dissolution" and "altered meaning," implying the importance of this particular circuit for the maintenance of "self" or "ego" and its processing of "meaning." Strong relationships were also found between the different imaging metrics, enabling firmer inferences to be made about their functional significance. This uniquely comprehensive examination of the LSD state represents an important advance in scientific research with psychedelic drugs at a time of growing interest in their scientific and therapeutic value. The present results contribute important new insights into the characteristic hallucinatory and consciousness-altering properties of psychedelics that inform on how they can model certain pathological states and potentially treat others.

LSD | serotonin | consciousness | brain | psychedelic

Lysergic acid diethylamide (LSD) is a potent serotonergic hallucinogen or "psychedelic" that alters consciousness in a profound and characteristic way. First synthesized in 1938, its extraordinary psychological properties were not discovered until 1943 (1). LSD would go on to have a major effect on psychology and psychiatry in the 1950s and 1960s; however, increasing recreational use and its influence on youth culture provoked the drug's being made illegal in the late 1960s. As a consequence, human research with LSD has been on pause for half a century. However, inspired by a revival of research with other psychedelics, such as psilocybin and ayahuasca, a small number of new reports on the psychological effects of LSD have recently been published (2–6).

LSD has a high affinity for a range of different neurotransmitter receptors, but its characteristic psychological effects are thought to

be mediated by serotonin 2A receptor (5-HT_{2A}R) agonism (7). Previous neurophysiological research with LSD is limited to electroencephalography (EEG) studies in the 1950s and 1960s. These reported reductions in oscillatory power, predominantly in the lower-frequency bands, and an increase in the frequency of alpha rhythms (8). Broadband decreases in cortical oscillatory power have been observed in modern EEG and magnetoencephalography (MEG) studies with psilocybin (9, 10), with EEG and the dimethyltryptamine-containing brew "ayahuasca" (11), and with rodent brain local-field potential recordings and a range of different 5-HT_{2A}R agonists (12–14).

The effects of psychedelics (other than LSD) on human brain activity have also previously been investigated with positron emission tomography (PET) (15) and functional magnetic resonance imaging (fMRI) (16). fMRI studies with psilocybin revealed decreased cerebral blood flow (CBF) and blood oxygen level-dependent (BOLD) signal in connector hubs (16), decreased

Significance

Lysergic acid diethylamide (LSD), the prototypical "psychedelic," may be unique among psychoactive substances. In the decades that followed its discovery, the magnitude of its effect on science, the arts, and society was unprecedented. LSD produces profound, sometimes life-changing experiences in microgram doses, making it a particularly powerful scientific tool. Here we sought to examine its effects on brain activity, using cutting-edge and complementary neuroimaging techniques in the first modern neuroimaging study of LSD. Results revealed marked changes in brain blood flow, electrical activity, and network communication patterns that correlated strongly with the drug's hallucinatory and other consciousness-altering properties. These results have implications for the neurobiology of consciousness and for potential applications of LSD in psychological research.

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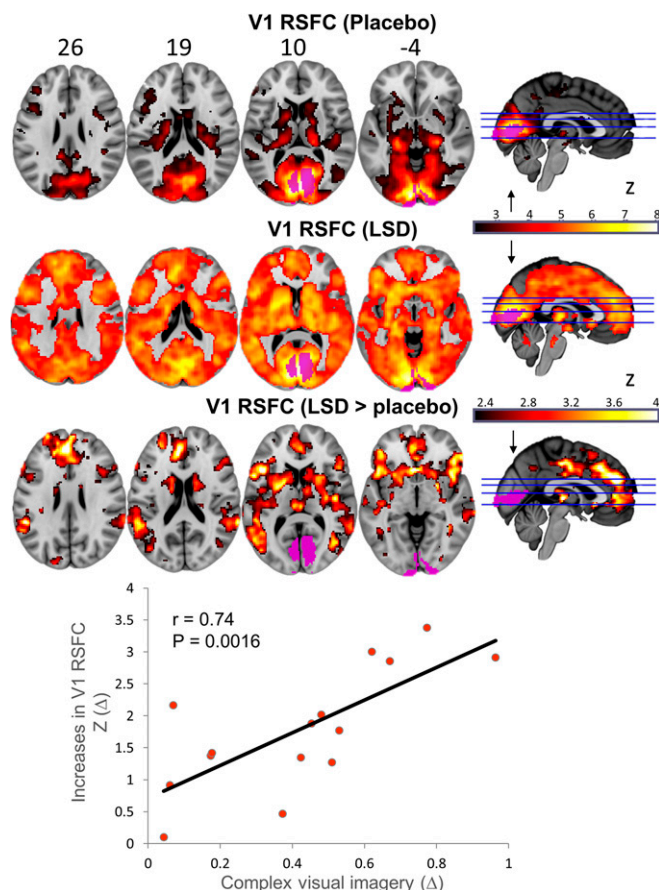


Fig. 2. Significant between-condition differences (orange = increases) in RSFC between the V1 seed region (purple) and the rest of the brain. Unthresholded maps can be viewed here: neurovault.org/collections/FBVSADVQ/ ($n = 15$).

Next, the effect of LSD on brain network properties was investigated. Twelve functionally familiar RSNs were identified in a set of 20 spatially independent components derived from independent data (human connectome project; [SI Appendix](#)). These RSNs are as follows: a medial visual network, a lateral visual network (VisL), an occipital pole network (VisO), an auditory network (AUD), a sensorimotor network, the DMN, a parietal cortex network (PAR), the dorsal attention network, the salience network, a posterior opercular network (POP), the left frontoparietal network, and the right frontoparietal network (rFPF).

Four metrics were calculated for each RSN: within-RSN CBF, within-RSN RSFC or “integrity,” within-RSN BOLD signal variance, and between-RSN RSFC or “segregation.” Between-condition differences in the first three metrics are shown in Fig. 4A, and the between-RSN RSFC results are shown in Fig. 4B. Differences (increases) in CBF were restricted to the visual RSNs, whereas differences in variance and integrity (decreases) were much more pronounced and universal. According to previous research with psilocybin (17), it was predicted that decreased DMN integrity (or DMN “disintegration”) would correlate with ratings of ego-dissolution, and this hypothesis was supported ($r = 0.49$; $P = 0.03$; *SI Appendix, Fig. S9G*). Given the large number of possible permutations, additional correlational analyses were not performed; however, to test the selectivity of the relationship between DMN disintegration and ego-dissolution, correlations were calculated for ego-dissolution and the integrity of the other 11 RSNs, and none were significant (*SI Appendix, Table S2*). Disintegration of the visual RSNs did not correlate with ratings of visual hallucinations. See *SI Appendix, Fig. S5*, for brain images of the RSN integrity results.

Between-RSN RSFC or RSN segregation was also markedly modulated by LSD. Decreased segregation (red squares with white

asterisks in Fig. 4B, right matrix) was observed between eight RSN pairs (VisL-PAR, VisL-dorsal attention network, VisO-POP, AUD-PAR, AUD-rFP, DMN-salience network, PAR-POP, POP-rFP), with only one pair (VisO-rFP) showing increased segregation (blue square with white asterisk in Fig. 4B, right matrix). Contrary to a prior hypothesis, decreased RSN segregation (in the eight networks that showed this effect) did not correlate with ratings of ego-dissolution ($r = 0.12$; $P > 0.05$).

Data from 14 volunteers were suitable for the MEG analyses (three females; mean age, 32.1 ± 8.3 y). Primary analyses focused on between-condition differences in frequency-specific oscillatory power, measured during eyes-closed rest. The relevant data (14 min of rest) were acquired ~ 50 min after completion of the MRI protocol and filtered into the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–15 Hz), beta (15–30 Hz), low gamma (31–49 Hz), and high gamma (51–99 Hz). Results revealed decreased oscillatory power under LSD in four frequency bands (Fig. 5A), with some suspected residual muscle artifact confounding the gamma results. For the lower-frequency bands (i.e., 1–30 Hz), the decreases reached significance in most of the sensors. To explore relationships between these outcomes and subjective measures, VAS ratings of ego-dissolution and visual hallucinations (simple and complex) were entered into regression analyses, using cluster permutation testing. Significant relationships were found between ego-dissolution and decreased delta (mean cluster, $r = -0.54$; $P < 0.05$) and alpha power (mean cluster, $r = -0.29$; $P < 0.05$) and between simple hallucinations and decreased alpha power (mean cluster, $r = -0.61$; $P < 0.05$) (Fig. 4B). Plotting the power spectrum independently for each condition for the significant alpha cluster (Fig. 5C), it is evident that the distribution of power is decreased across a broad frequency

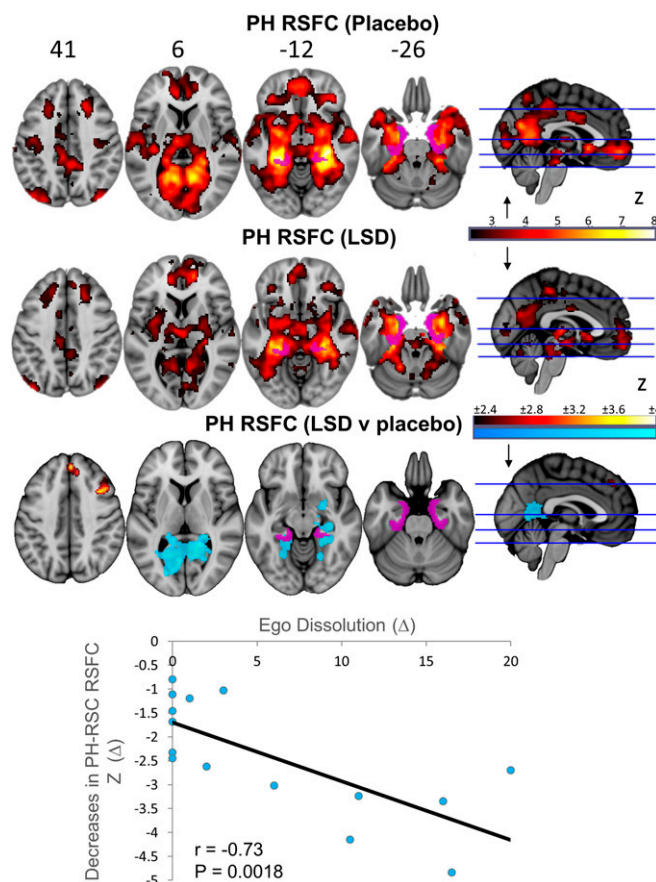


Fig. 3. Significant between-condition differences in RSFC between the PH seed and the rest of the brain (orange = increases; blue = decreases). Unthresholded maps can be viewed here: neurovault.org/collections/FBVSAVDQ/ ($n = 15$).

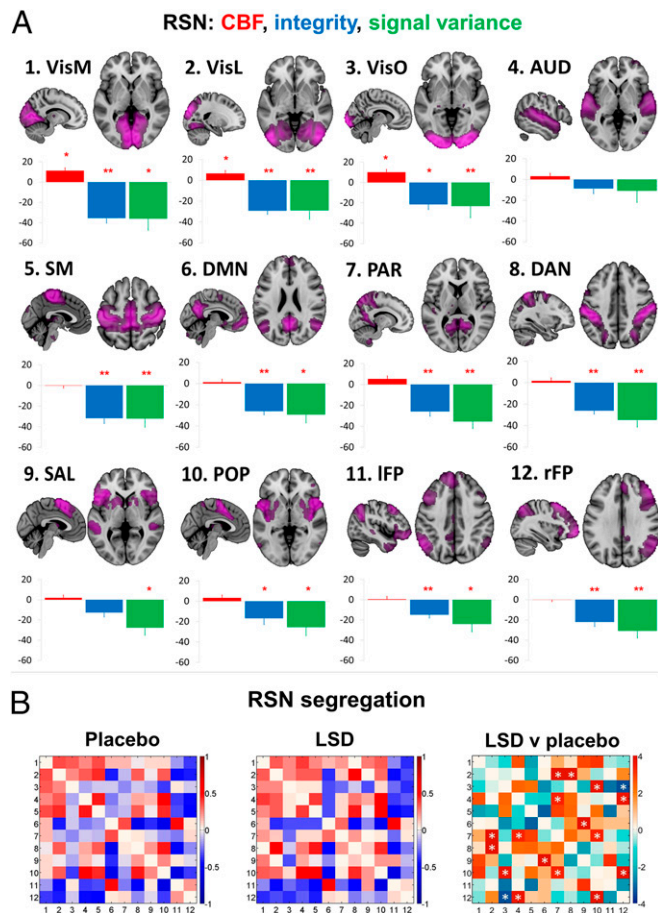


Fig. 4. (A) Mean percentage differences (\pm SEM) in CBF (red), integrity (blue), and signal variance (green) in 12 different RSNs under LSD relative to placebo (red asterisks indicate statistical significance, $*P < 0.05$; $**P < 0.01$, Bonferroni corrected). (B) Differences in between-RSN RSFC or RSN “segregation” under LSD vs placebo. Each square in the matrix represents the strength of functional connectivity (positive = red, negative = blue) between a pair of different RSNs (parameter estimate values). The matrix on the far right displays the between-condition differences in covariance (t values): red = reduced segregation and blue = increased segregation under LSD. White asterisks represent significant differences ($P < 0.05$, FDR corrected; $n = 15$).

range under LSD, and the peak alpha rhythm is reduced in amplitude and of higher frequency (i.e., 10 Hz under placebo, 12 Hz under LSD; $t = 4.21$; $P = 0.0009$). Source modeling revealed that sources of the power decreases were relatively distributed throughout the brain (*SI Appendix, Table S8*), with significant effects in the PCC/precuneus (theta, alpha, and beta) and other high-level cortical regions (delta-beta).

This study's multimodal design enabled correlational analyses to be performed between the various (significant) imaging outcomes. This was done in a hypothesis-driven manner, and because the outcomes' directions were already known, one-tailed tests were performed. Relationships were observed between the increases in CBF (localized to the visual cortex) and decreases in alpha power in posterior (occipital cortex) sensors ($r = -0.59$; $P = 0.029$; *SI Appendix, Fig. S6*) and between increases in V1 RSFC (to the most significant regions: $P < 0.01$; 5,000 permutations; *SI Appendix, Fig. S8*) and decreased posterior-sensor alpha power ($r = -0.81$; $P = 0.0015$; *SI Appendix, Fig. S6*), but there was only a trend-level relationship between increases in visual cortex CBF and increases in V1 RSFC ($r = 0.43$; $P = 0.055$). The mean change (decreases) in the integrity of the 12 RSNs correlated very strongly with the mean change (decreases) in their variance ($r = 0.89$; $P = 4 \times 10^{-6}$; *SI Appendix, Fig. S6*). Neither metric correlated with the mean change

in CBF, however [$r = 0.1$ ($P > 0.05$) and $r = 0.33$ ($P > 0.05$) for integrity and variance, respectively], nor head motion (*SI Appendix*), but they did correlate with the mean decrease in power (significant sensors) for the four displayed frequency bands [$r = 0.79$ ($P = 0.001$; *SI Appendix, Fig. S6*) and $r = 0.76$ ($P = 0.002$) for integrity and variance, respectively]. Mean decreases in RSN segregation (for the eight pairs that showed this effect) correlated with mean decreases in RSN integrity (mean of all 12 RSNs, $r = 0.53$; $P = 0.02$; *SI Appendix, Fig. S6*) and reduced oscillatory power (delta-beta combined, $r = 0.67$; $P = 0.017$; *SI Appendix, Fig. S6*), but not decreased RSN variance ($r = 0.33$, $P > 0.05$) nor increased CBF ($r = 0.18$; $P > 0.05$). Given the number of possible permutations, we chose not to explore beyond these relationships.

Discussion

The present findings offer a comprehensive new perspective on the changes in brain activity characterizing the LSD state, enabling us to make confident new inferences about its functional neuroanatomy. Principal findings include increased visual cortex CBF, RSFC, and decreased alpha power, predicting the magnitude of visual hallucinations; and decreased DMN integrity, PH-RSC RSFC, and delta and alpha power (e.g., in the PCC), correlating with profound changes in consciousness, typified by ego-dissolution. More broadly, the results reinforce the view that resting state ASL, BOLD FC, and MEG measures can be used to inform on the neural correlates of the psychedelic state (9, 16). Importantly, strong relationships were found between the different imaging measures, particularly between changes in BOLD RSFC (e.g., network “disintegration” and “desegregation”) and decreases in oscillatory power, enabling us to make firmer inferences about their functional meaning.

The present study sheds new light on the relationship between changes in spontaneous brain activity and psychedelic-induced visual hallucinations. Strong relationships were observed between increased V1 RSFC and decreased alpha power, as well as ratings of both simple and complex visual hallucinations. The latter result is consistent with previous findings with psilocybin (29). Importantly, a very strong relationship was also observed between increased V1 RSFC and decreased alpha power in occipital sensors, suggesting that as well as being commonly related to visual hallucinations, these physiological effects are closely interrelated. The increase in V1 RSFC under LSD is a particularly novel and striking finding and suggests that a far greater proportion of the brain contributes to visual processing in the LSD state than under normal conditions. This expansion of V1 RSFC may explain how normally discreet psychological functions (e.g., emotion, cognition, and indeed the other primary senses) can more readily “color” visual experience in the psychedelic state.

Biologically informed modeling has suggested that instability within the primary visual cortex may facilitate the emergence of geometric hallucinations via self-organized patterns of neural excitation (30), and eyes-closed fMRI recordings during ayahuasca hallucinations suggest the visual cortex behaves “as if” there is external input when there is none (31) (see also ref. 29). The present findings of increased visual cortex CBF, expanded V1 RSFC, and decreased alpha power may be seen as consistent with the notion of “seeing with eyes-shut” under psychedelics, because they are all properties normally associated with visual stimulation (32, 33). Cortical alpha has been hypothesized to serve a general inhibitory function, filtering out “stimulus-irrelevant” information (34). Thus, reduced alpha power (9, 29, 35) could have disinhibitory consequences, facilitating the release of anarchic patterns of excitation that manifest spontaneously and experientially as visual hallucinations. This hypothesis is lent (indirect) support by two prior studies that found reduced spontaneous visual cortex alpha power under psilocybin alongside reduced evoked visual responses (9, 29). Further work, using higher-resolution brain imaging, machine learning techniques, dynamic measures of functional and effective connectivity, and improved “capture” of visual hallucinations (e.g., via button press or experience sampling), may help to develop this appealing model (e.g., see ref. 36).

(43). For this reason, more direct measures of neural activity (e.g., EEG and MEG) and/or more dynamic fMRI measures (e.g., RSFC) should be considered more reliable indices of the functional brain effects of psychedelics, and it is notable in this regard that our previous MEG (9) and RSFC (16, 19, 42) findings with psilocybin are highly consistent with those observed here with LSD. Thus, rather than speculate on the above-mentioned discrepancy, it may be more progressive to highlight the advantages of EEG/MEG and dynamic fMRI and conclude that further work would be required to resolve discrepancies in the literature regarding the effects of psychedelics on metabolically related metrics that lack temporal resolution.

Finally, as evidence supporting the therapeutic potential of psychedelics mounts (6, 44–46), so does our need to better understand how these drugs work on the brain. In many psychiatric disorders, the brain may be viewed as having become entrenched in pathology, such that core behaviors become automated and rigid. Consistent with their “entropic” effect on cortical activity (17), psychedelics may work to break down such disorders by dismantling the patterns of activity on which they rest. Future work is required to test this hypothesis and the others that have been

presented here as part of a broader initiative to properly utilize these valuable scientific tools.

Methods

This study was approved by the National Research Ethics Service committee London-West London and was conducted in accordance with the revised declaration of Helsinki (2000), the International Committee on Harmonization Good Clinical Practice guidelines, and National Health Service Research Governance Framework. Imperial College London sponsored the research, which was conducted under a Home Office license for research with schedule 1 drugs. For more methods see *SI Appendix, Methods*.

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